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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/044,650	01/11/2002	Beth A. Goins	UTSK:343US/TMB	9390

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Thomas M. Boyce, Esq.
FULBRIGHT & JAWORSKI L.L.P.
Suite 2400
600 Congress Avenue
Austin, TX 78701

EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/044,650	GOINS ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/24/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election with traverse of the species radioisotope as a diagnostic agent, and the species DSPC is acknowledged in the response filed November 7, 2003.

Applicant mainly traverses that it would not be unduly burdensome for the examiner to search and/or consider the patentability of the presently pending claims. The traversal is found partially persuasive for a search and/or consider the patentability of the species therapeutic agent, cytotoxic agent and the above elected species. However, a search of the elected species or even a generic claim does not necessarily overlap with that of all of the remaining non-elected species. For example, prodrugs are not the same in any to applicant's elected species dye. The same speaks for hormone suppressants.

Thus, the restriction requirement as modified by the reasons set forth in the immediately preceding paragraph remains proper, and thus, is made final.

Claims 1-30 are pending for examination.

The examiner notes that the transmittal letter dated 1/11/02 specifically request an amendment to add the cross-reference information as the first paragraph of the as-filed specification. However, the added priority information contains typographical errors: The phrase "which claims priority of then co-pending U.S. Provisional Application No.: 06,143,742, filed July 14, 1999" is not correct. Applicant is requested changed the present phrase to -- which claims priority under 119(e) to U.S. Provisional Application No. 60/143,742, filed July 14, 1999 --.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method for delivery and retention of an active agent in one or more targeted lymph nodes, comprising:

a) injecting into a mammal a first composition comprising a ligand complexed to a colloidal particle having the diameter of less than 500 nm; and

b) injecting to said mammal a second composition comprising an anti-ligand which binds to said ligand,

wherein an active agent is conjugated to either said colloid or said anti-ligand,

and whereby the anti-ligand encounters and causes aggregation of the colloid-ligand complex at , or just prior to reaching, the one or more targeted lymph nodes.

. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The main thrust of the invention is the concept of injecting two compositions to a mammal in order to target the delivery of any known bioactive agent to lymph nodes, wherein the first injected composition comprises a colloid particle coated with a ligand,

e.g., biotin, and wherein the second injected composition comprises an anti-ligand, *e.g.*, avidin. The state of the art of targeted delivery to lymph nodes by using a generic colloid-base system is not conventional and routine at the time the invention was made, see the references cited in the second full par. on page 6 of the specification, Moghimi, Prog, Biophys. Molec. Biol., Vol. 65, 3, pp. 221-249, 1996 (IDS), Oussoren, Biochimica et Biophysica Acta 1328, 261,272, 1997. One of the important issues that were raised in the cited references including the as-filed specification is the influence of a colloid particle size, its contents. The as-filed specification clearly teaches such on page 13, and specifically states that "if the colloid-ligand composition is too large, it is retained at the site of injection", and that "if the colloid-ligand composition is too small, it is transported from the site of injection into the circulation and is not retained in the lymph nodes". However, the claims as presently pending embrace the use of an enormous number of colloid particles, regardless of their sizes, in order to achieve the targeted delivery of a bioactive agent to lymph nodes for a sufficient amount of time required for the agent's activity. In fact, Oussoren teaches and provides factual evidence (Figure 3A) demonstrating that only smaller liposomes (less than 400 nm in mean size) were able to enter the lymphatic capillaries, and that even with the liposomes with the 400 nm in mean size, roughly more than 80% of the contents remain at the injected site. None of the working examples employs liposomes with mean sizes larger than 500 nm. Thus, given the fact that detailed information on factors influencing lymphatic targeted drug delivery remains unsettled within the those of skill in the art, that the as-filed specification does not provide any solution to the criticality of the colloidal size, and

given the reasons set forth, one skilled in the art would not have been able to reasonably extrapolates, from the teachings and/or working examples provided by the specification to the entire breadth of the claimed invention.

Another issue which is essential for the usage within the context of the specification is the teaching provided by the specification on page 15, which clearly teaches that in order for the targeted delivery to the lymph nodes to work, the two compositions must be injected within a sufficient amount of time and/or at locations, so that the injected anti-ligand would encounter the colloid-ligand at, or just prior to reaching, the targeted lymph node, whereby such encounter would cause aggregation of the colloid-ligand and its subsequent retention at the targeted lymph nodes. As such, the claims are only reasonably enabling for claimed emobodiments, wherein such steps are employed in order to have the injected anti-ligand encountering the colloid-ligand at, or just prior to reaching, the targeted lymph node.

With respect to the breadth of presently pending claims, which encompasses numerous ligands and anti-ligands other than biotin and avidin, and colloid based systems other than liposomes, Philips WT, (abstract, July 16, 1999, 9th Annual Smposium on Cancer Research in San Antonio, IDS) teaches:

The avidin injection causes aggregation of the biotin coated liposomes that are in the processof migrating through lymphatic vessels. When this aggregated liposome complex reaches the next encountered lymph node, it becomes retained for a prolonged time in this node. This prolonged retention contrasts greatly with control liposome preparations which simply pass through the lymph node without retention.

The specification on pages 23 and 24 acknowledges the same as indicated above by Philips WT.

Thus, it is apparent to one skill in the art, particularly on the basis of the teaching provided by the specification and the state of the art exemplified by Philips, that the aggregation property caused by the injected anti-ligand is essential for the targeted delivery and retention a colloidal delivery system as claimed. Thus, the presently pending claims are only reasonably enabling for such claimed embodiments, wherein a combination of a colloidal particle (such as nanoparticles, microparticles, microcapsules, dendrimers, lipid based particles) with a size range of less than 500 nm, and of ligan/anti-ligand, all of which exhibit the property of being able to conjugate and to cause aggregation of the injected complexes prior to their entry into the targeted lymph nodes through the lymphatic system.

In view of reasons set forth above, it would require an undue experimentation for one skilled in the art to practice the full breadth of the claimed invention at the time the invention was made.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another

> filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 20-27 are rejected under 35 USC 102(b) as being anticipated by Allen (US Pat No. 5,527,528).

The claims are simply directed to a kit or composition, each of which comprises a composition comprising a ligand (biotin-liposome or avidin-liposome), and another

composition comprising an ani-ligand, wherein an active agent is present in either the ligand containing composition or in the anti-ligand containing composition. Allen teaches the same throughout the disclosure, particularly abstract, column 9, lines 29-36, column 10, lines 17-27, column 12, and column 20. Specifically, the composition or kit of Allen comprises: an anti-ligand, a ligand conjugated to a liposome which entrapped a therapeutic agent and/or a radioisotope. Also column 12, for example, discloses that a kit comprising a composition comprising a ligand (avidin) conjugated to a therapeutic agent/diagnostic agent entrapped liposome and another composition comprising an anti-ligand (biotin, for example) conjugated to a tumor specific antibody as an active agent. The liposome of Allen is preferably a derivatized vesicle-forming lipid, which includes DSPC (PC based lipid coated with a polymer such as PEG). Means of employing the compositions for imaging or therapeutic application are disclosed throughout the reference.

Claims 25 and 28 are rejected under 35 USC 103(a) as being unpatentable over Allen taken with Phillips (US Pat No. 5,143,713), and Griffiths (US Pat No. 5,482,698).

The rejection of the base claim under 35 USC 102(b) is applied here as indicated above. To the extent that Allen does not teach the use of a combination of glutathione, 99mTC-HMPAO, and a blue dye for enhancing the stability of a delivery agent and/or imaging assays, Phillips teaches the same throughout the reference, particularly column 5, and Example 1, which teaches DSPC as a preferred liposome.

It would have been obvious for one of ordinary skill in the art to employ a radioisotope labeled liposome as disclosed in Phillips in any of the components employed in a ligand/antibody conjugate or the lipid based carrier in Allen. One of ordinary skill in the art would have been motivated to employ the radioisotope labeled liposome as disclosed in Phillips as the lipid based carrier conjugated to either a ligand or anti-ligand in the method of Allen in order to enhance the stability of the delivered agent and at the same time provides an stabilized imaging agent for monitoring the distribution of the delivered agent at the targeted tumor sites.

Claim 28 also embraces an incorporation of a blue dye in the labeled liposomal composition. However, the utilization of any fluorescent dye as a detection agent so as to monitor the distribution of the delivered agent during its circulation *in vivo* is well known in the prior art as exemplified in Griffiths, (column 14, lines 31-47). As such, it would then have been obvious for one of ordinary skill in the art to employ a dye such as a blue dye in any of the delivered agent contained in the delivered composition. One would have been motivated to do so because the prior art of record as a whole, see Griffiths, for example, teaches that the utilization of any fluorescent dye as a detection agent in a biotin/avidin colloidal particle is conventional in the prior art and that such use would provide a convenient step to visually monitor the distribution of the delivered agent during its circulation *in vivo.*

Thus, the claimed invention was *prima facie* obvious.

Claims 1-19, 29-30 are rejected under 35 USC 103 as being unpatentable over Allen taken with either Griffiths or Gustavson (US Pat No. 5,420,105), and further in view of Oussoren (Biochimica et Biophysica, 1328, 261272, 1997, IDS).

Allen teaches a method of delivering a first composition comprising a ligand conjugated to a tumor specific antibody to a mammal, and delivering to the mammal another composition comprising an anti-ligand/therapeutic agent/diagnostic agent containing liposomal carriers, wherein the liposomal carriers having the sizes predominantly in the range 0.05 to 0.12 microns (abstract, column 6, lines 44-59, column 7 bridging column 8, column 9, lines 29-36, column 10, lines 17-27, column 12, and column 20). Specifically, the ligand/anti-ligand binding pair is biotin and avidin, or avidin and biotin, respectively. Column 12, for example, discloses that a first delivered composition comprises a ligand, biotin, for example, conjugated to a tumor specific antibody as an active agent. Column 12 also discloses that a second delivered composition comprises an anti-ligand (avidin) conjugated to a therapeutic agent/diagnostic agent entrapped liposome. The liposome of Allen is preferably a derivatized vesicle-forming lipid, which includes DSPC (PC based lipid coated with a polymer such as PEG, column 5). Means of employing the compositions for imaging or therapeutic application are disclosed throughout the reference, especially column 11, lines 32-61. Allen specifically teaches that the liposomal composition is utilized specifically for tumor treatment, especially blood-born tumors. The active agent can also include a radioisotope as an imaging agent (column 12, last par.).

Allen does not teach explicitly that the liposomal particle can also be used to enhance the delivery of the first composition comprising a tumor specific antibody conjugated to a ligand such as biotin, nor does Allen teaches that a dye can be used to enhance the visualization of the delivered agents in a treated subject.

However, both Griffiths and Gustavson teach that a colloidal based system such as a biocompatible polymeric carrier containing a biotin or avidin is effective to increase the targeting of both a ligand conjugate or a subsequent anti-ligan conjugate at an intended target site such as a tumor site (Griffiths, abstract, column 7, lines 32-36, column 8; Gustavson, column 3, column 14, lines 8-15).

It would have been obvious for one of ordinary skill in the art to employ a colloidal based delivery carrier to enhance the delivery and binding of ligand/anti-ligand at a target tumor site to which the first delivered ligand is bound. One of ordinary skill in the art would have been motivated to employ any known colloidal based delivery carrier in the ligand conjugate of Allen. One of ordinary skill in the art would have been motivated to employ a colloidal particle such as those described in Griffiths or Gustavson because such incorporation of the particle to a ligand and/or anti-ligand would not only enhance the delivery and stability of the antibody during its traversal to an intended target tumor site, but also provides an increased number of binding sites to which a subsequently administered composition such as the avidin/therapeutic agent/imaging agent/liposome can bind, thereby amplifying the amount of detection or therapeutic agent at the target tumor site.

In the event that one of ordinary skill in the art would employ the delivered composition to target blood born tumor sites such as leukemia, wherein metastases are already formulated, as taught by Allen, one would have a reasonable expectation of success in having the liposomal composition of Allen localized and retained at any tumor site in a leukemia patient such as those residing in lymph nodes because of the evidences and teachings provided by Oussoren, which clearly teaches that colloidal particles up to about .4 um in diameter are transported from an injection site into the lymphatic capillaries and localized in regional lymph nodes (Figure 3).

It would also have been obvious for one of ordinary skill in the art to employ a radioisotope as an imaging detector in any of the components employed in a ligand/antibody conjugate or the lipid based carrier in Allen taken with Griffiths or Gustavson. One of ordinary skill in the art would have been motivated to employ a radioisotope in either the antibody conjugated with a colloidal particle or the lipid based carrier because the prior art of record as a whole, exemplified by Allen, teaches that the use of a radioisotope would provide an stabilized imaging agent for visualizing the distribution of the delivered agent at the targeted tumor sites.

Thus, the claimed invention was *prima facie* obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0184.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center number, which is **703-872-9306.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

DAVE T. NGUYEN
PRIMARY EXAMINER